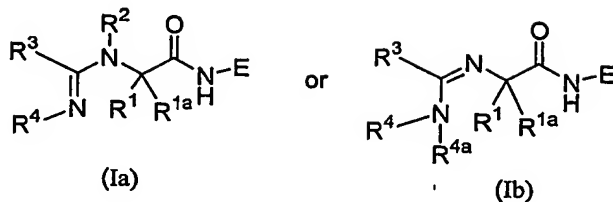


## WE CLAIM:

1. A compound of Formula (Ia) or (Ib):



5 wherein:

E is:

- (i)  $-C(R^5)(R^6)X^1$  where  $X^1$  is  $-CHO$ ,  $-C(R^7)(R^8)CF_3$ ,  $-C(R^7)(R^8)CF_2CF_2R^9$ ,  $-C(R^7)(R^8)R^{10}$ ,  $-CH=CHS(O)_2R^{10}$ ,  $-C(R^7)(R^8)C(R^7)(R^8)OR^{10}$ ,  $-C(R^7)(R^8)CH_2OR^{10}$ ,  $-C(R^7)(R^8)C(R^7)(R^8)R^{10}$ ,  $-C(R^7)(R^8)CH_2N(R^{11})SO_2R^{10}$ ,  $-C(R^7)(R^8)CF_2C(O)NR^{10}R^{11}$ ,  $-C(R^7)(R^8)C(O)NR^{10}R^{11}$ ,  $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2OR^{11}$ ,  $-C(R^7)(R^8)C(O)N(R^{11})(CH_2)_2NR^{10}R^{11}$ ; or
- (ii)  $-C(R^{5a})(R^{6a})CN$ ;
- 10

where:

$R^5$  and  $R^{5a}$  are independently hydrogen or alkyl; and

- 15  $R^6$  and  $R^{6a}$  are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, carboxyalkyl, alkoxy carbonylalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, cyano,  $-alkylene-X-R^{12}$  (where X is  $-O-$ ,  $-NR^{13}-$ ,  $-CONR^{13}-$ ,  $-S(O)_{n1}-$ ,  $-NHCO-$ ,  $-CO-$ , or  $-C(O)O-$  where  $n1$  is 0-2, and  $R^{12}$  and  $R^{13}$  are independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl) wherein the aromatic or alicyclic ring in  $R^6$  and  $R^{6a}$  is optionally substituted with one, two, or three  $R^a$  independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxy carbonyl, amino, monsubstituted amino, disubstituted amino, nitro, aryloxy, benzyloxy, acyl, or arylsulfonyl where the aromatic or alicyclic ring in  $R^a$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxy carbonyl; or
- 20
- 25

$R^5$  and  $R^6$  and  $R^{5a}$  and  $R^{6a}$  taken together with the carbon atom to which both  $R^5$  and  $R^6$  and  $R^{5a}$  and  $R^{6a}$  are attached form (i) cycloalkylene optionally substituted with one or two  $R^b$  independently selected from alkyl, halo, alkylamino, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxy carbonyl, or aryloxy carbonyl, or (ii) heterocycloalkylene optionally substituted with one to four  $R^c$  which are independently selected

30



from alkyl, haloalkyl, hydroxy, hydroxyalkyl, alkoxyalkyl, alkoxyalkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl,  $-S(O)_{n2}R^{14}$ ,  $-alkylene-S(O)_{n2}-R^{15}$ ,  $-COOR^{16}$ ,  $-alkylene-COOR^{17}$ ,  $-CONHR^{18}R^{19}$ , or  $-alkylene-CONHR^{20}R^{21}$  (where  $n2$  is 0-2 and  $R^{14}$ - $R^{17}$ ,  $R^{18}$  and  $R^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocyclyl and  $R^{19}$  and  $R^{21}$  are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to cycloalkylene or heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monsubstituted amino, disubstituted amino, or acyl;

$R^7$  is hydrogen or alkyl;

$R^8$  is hydroxy; or

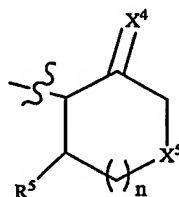
$R^7$  and  $R^8$  together form oxo;

$R^9$  is hydrogen, halo, alkyl, aralkyl or heteroaralkyl; and

$R^{10}$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, or heterocyclylalkyl wherein the aromatic or alicyclic ring in  $R^{10}$  is optionally substituted with one, two, or three  $R^d$  independently selected from alkyl, haloalkyl, alkoxy, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, aryl, heteroaryl, amino, monsubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in  $R^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, or dialkylamino; and

$R^{11}$  is hydrogen or alkyl; or

(iii) a group of formula (a):



(a)

where:

$n$  is 0, 1, or 2;

$X^4$  is selected from  $-NR^{22}$ -,  $-S$ -, or  $-O$ - where  $R^{22}$  is hydrogen, alkyl, or alkoxy; and

$X^5$  is  $-O$ -,  $-S$ -,  $-SO_2$ -, or  $-NR^{23}$ - where  $R^{23}$  is selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl,



heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,  $-S(O)_2R^{24}$ ,  $-alkylene-S(O)_{n3}-R^{25}$ ,  $-COOR^{26}$ ,  $-alkylene-COOR^{27}$ ,  $-CONR^{28}R^{29}$ , or  $-alkylene-CONR^{30}R^{31}$  (where  $n3$  is 0-2 and  $R^{24}$ ,  $R^{27}$ ,  $R^{28}$  and  $R^{30}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, or heterocyclylalkyl and  $R^{29}$  and  $R^{31}$  are independently hydrogen or alkyl) where the aromatic or alicyclic ring in  $X^5$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl;

$R^5$  is as defined above;

$R^1$  is hydrogen or alkyl;

$R^{1a}$  is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclylalkyl, or  $-alkylene-X-R^{32}$  [wherein  $X$  is  $-NR^{33}-$ ,  $-O-$ ,  $-S(O)_{n4}-$ ,  $-CO-$ ,  $-COO-$ ,  $-OCO-$ ,  $-NR^{33}CO-$ ,  $-CONR^{33}-$ ,  $-NR^{33}SO_2-$ ,  $-SO_2NR^{33}-$ ,  $-NR^{33}COO-$ ,  $-OCONR^{33}-$ ,  $-NR^{33}CONR^{34}$ , or  $-NR^{33}SO_2NR^{34}$  (where  $R^{33}$  and  $R^{34}$  are independently hydrogen, alkyl, or acyl and  $n4$  is 0-2) and  $R^{32}$  is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl] wherein said alkylene chain is optionally substituted with one to six halo and wherein the aromatic or alicyclic ring in  $R^{1a}$  is optionally substituted with one, two, or three  $R^e$  independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, monosubstituted amino, disubstituted amino, or acyl; or

$R^1$  and  $R^{1a}$  together with the carbon atoms to which they are attached form cycloalkylene or heterocycloalkylene ring wherein said cycloalkylene or heterocycloalkylene is optionally substituted with one or two  $R^f$  independently selected from alkyl, halo, hydroxyalkyl, keto, or  $-SO_2R^{39}$  where  $R^{39}$  is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl where the aromatic or alicyclic ring in  $R^f$  is optionally substituted with one, two, or three substituents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, halo, carboxy, or alkoxycarbonyl;

$R^2$  is hydrogen or alkyl;

$R^3$  is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, amino, mono or disubstituted amino, or  $-alkylene-X^3-R^{35}$  [wherein  $X$  is  $-NR^{36}-$ ,  $-O-$ ,  $-S(O)_{n5}-$ ,  $-CO-$ ,  $-COO-$ ,  $-OCO-$ ,  $-NR^{36}CO-$ ,  $-CONR^{36}-$ ,  $-NR^{36}SO_2-$ ,  $-SO_2NR^{36}-$ ,  $-NR^{36}COO-$ ,  $-OCONR^{36}-$ ,  $-NR^{36}CONR^{37}-$ , or  $-NR^{36}SO_2NR^{37}-$  (where  $R^{36}$  and  $R^{37}$  are independently hydrogen, alkyl, or acyl and  $n5$  is 0-2) and  $R^{35}$  is hydrogen, alkyl, haloalkyl,



cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl] wherein the aromatic or alicyclic rings in  $R^3$  are optionally substituted by one, two, or three  $R^g$  independently selected from alkyl, halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, oxo, cyano, nitro, acyl, acyloxy, aryl, heteroaryl, cycloalkyl, heterocyclyl, aryloxy, benzyloxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfonyl, arylsulfinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, amino, monosubstituted or disubstituted amino, and further wherein the aromatic and alicyclic rings in  $R^g$  are optionally substituted with one, two, or three  $R^h$  wherein  $R^h$  is independently selected from alkyl, halo, haloalkyl, haloalkoxy, hydroxy, nitro, cyano, hydroxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylthio, alkylsulfonyl, amino, alkylamino, dialkylamino, aryl, heteroaryl, cycloalkyl, carboxy, carboxamido, or alkoxycarbonyl;

$R^4$  is  $-S(O)_2R^{38}$  where  $R^{38}$  is phenyl or naphthyl optionally substituted with one, two, or three  $R^i$  independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, monosubstituted amino, disubstituted amino, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, heterocyclyl, aryloxycarbonyl, heteroaryloxycarbonyl, aryloxy, heteroaryloxy,  $-NHSO_2R^j$  where  $R^j$  is alkyl, aryl, or heteroaryl,  $-SO_2NR^kR^l$  where  $R^k$  is hydrogen or alkyl and  $R^l$  is alkyl, aryl, heteroaryl, hydroxyalkyl, alkoxyalkyl, or aminoalkyl,  $-NHCOOR^m$  where  $R^m$  is alkyl, aryl, or heteroaryl, or  $-NHCONR^nR^o$  where  $R^n$  and  $R^o$  are independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; where the aromatic or alicyclic ring in  $R^i$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl;

$R^{4a}$  is hydrogen, alkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, alkoxy, hydroxy, aryl, aralkyl, aroyl, heteroaryl, heteroaralkyl, heteroaroyl,  $-C(O)OR^{40}$  where  $R^{40}$  is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, or aralkyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, or cycloalkyl wherein the aromatic rings in  $R^{4a}$  are optionally substituted with one, two or three halogen, hydroxy, alkyl, alkoxy, haloalkyl, haloalkoxy, carboxy, nitrile, nitro, or  $-CONH_2$ ; or a pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein  $R^4$  is  $-S(O)_2R^{38}$  where  $R^{38}$  is phenyl or naphthyl optionally substituted with one, two, or three  $R^i$  independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl,



amino, monosubstituted amino, disubstituted amino, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, or heterocyclyl where the aromatic or alicyclic ring in  $R^i$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl.

3. The compound of Claim 1 or 2 wherein E is  $-C(R^5)(R^6)X^1$  in which:

$R^5$  is hydrogen or alkyl; and

$R^6$  is hydrogen, alkyl,  $-(alkylene)-OR^{12}$  (where  $R^{12}$  is hydrogen, alkyl or haloalkyl), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl wherein the aromatic or alicyclic ring in aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl is optionally substituted with one, two, or three  $R^a$  independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monosubstituted amino, disubstituted amino, or acyl.

4. The compound of Claim 1 or 2 wherein:

$R^5$  is hydrogen;

$R^6$  is ethyl; and

$X^1$  is  $-CHO$ ,  $-C(O)R^{10}$ ,  $-C(O)CF_3$ ,  $-C(O)CF_2CF_2R^9$ ,  $-CH=CHS(O)_2R^{10}$ ,  $-C(O)CF_2C(O)NR^{10}R^{11}$ ,  $-C(O)C(O)NR^{10}R^{11}$ ,  $-C(O)CH_2OR^{10}$ ,  $-C(O)CH_2N(R^{11})SO_2R^{10}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2OR^{11}$ ,  $-C(O)C(O)N(R^{11})(CH_2)_2NHR^{11}$  or  $-C(O)C(O)R^{10}$ ; wherein  $R^{10}$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkylalkyl or heterocyclylalkyl wherein the aromatic ring is optionally substituted with  $R^d$  selected from heteroaryl, aryl, or alkyl,  $R^{11}$  is hydrogen or alkyl and  $R^9$  is halo.

5. The compound of Claim 1 or 2 wherein E is  $-CHR^6C(O)R^{10}$  where  $R^6$  is ethyl, propyl, or butyl, and  $R^{10}$  is heteroaryl optionally substituted with one or two  $R^d$  independently selected from alkyl, haloalkyl, alkoxy, cycloalkyl, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, aryl, heteroaryl, amino, monosubstituted amino, disubstituted amino, or acyl wherein the aromatic or alicyclic ring in  $R^d$  is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, haloalkoxy, halo, hydroxy, carboxy, alkoxycarbonyl, amino, alkylamino, or dialkylamino.

6. The compound of Claim 1 or 2 wherein E is  $-CH_2CN$ .

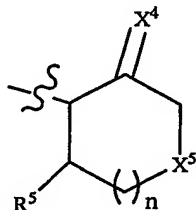
7. The compound of Claim 1 or 2 wherein E is  $-CR^{5a}R^{6a}CN$  where  $R^{5a}$  and  $R^{6a}$  together with the carbon atom to which they are attached form cycloalkylene optionally substituted with one or two  $R^b$  independently selected from alkyl, halo, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxycarbonyl, or aryloxycarbonyl.



8. The compound of Claim 1 or 2 wherein E is  $-\text{CR}^{5a}\text{R}^{6a}\text{CN}$  where  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene optionally substituted with one or two  $\text{R}^b$  independently selected from alkyl, halo, dialkylamino, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, alkoxycarbonyl, or aryloxycarbonyl.

9. The compound of Claim 1 or 2 wherein E is  $-\text{CR}^{5a}\text{R}^{6a}\text{CN}$  where  $\text{R}^{5a}$  and  $\text{R}^{6a}$  together with the carbon atom to which they are attached form heterocycloalkylene optionally substituted with one to two  $\text{R}^c$  which are independently selected from alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aminoalkyl, acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,  $-\text{S}(\text{O})_{n2}\text{R}^{14}$ ,  $-\text{alkylene-S}(\text{O})_{n2}\text{R}^{15}$ ,  $-\text{COOR}^{16}$ ,  $-\text{alkylene-COOR}^{17}$ ,  $-\text{CONHR}^{18}\text{R}^{19}$ , or  $-\text{alkylene-CONHR}^{20}\text{R}^{21}$  (where  $n2$  is 0-2 and  $\text{R}^{14}$ - $\text{R}^{17}$ ,  $\text{R}^{18}$  and  $\text{R}^{20}$  are independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, or heterocyclyl and  $\text{R}^{19}$  and  $\text{R}^{21}$  are independently hydrogen or alkyl) wherein the aromatic or alicyclic ring in the groups attached to heterocycloalkylene is optionally substituted with one, two, or three substituents independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, carboxy, alkoxycarbonyl, amino, monsubstituted amino, disubstituted amino, or acyl.

10. The compound of Claim 1 or 2 wherein E is:



in which:

$n$  is 0, 1, or 2,  $\text{X}^4$  is  $-\text{NR}^{22}$ -,  $-\text{O}-$  or  $-\text{S}-$  where  $\text{R}^{22}$  is hydrogen, alkyl, or alkoxy;  $\text{X}^5$  is  $-\text{O}-$ ,  $-\text{S}(\text{O})_2$ -,  $-\text{S}-$  or  $-\text{NR}^{23}$ - where  $\text{R}^{23}$  is selected from hydrogen, alkyl,  $-\text{S}(\text{O})_2\text{R}^{24}$ ,  $-\text{C}(\text{O})\text{OR}^{26}$ , or acyl, where  $\text{R}^{24}$  is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl and  $\text{R}^{26}$  is hydrogen or alkyl.

11. The compound of any of the Claims 1-10 wherein:

$\text{R}^1$  is hydrogen; and

$\text{R}^{1a}$  is alkyl, cycloalkyl, aralkyl, heteroaralkyl, cycloalkylalkyl, heterocyclylalkyl, or  $-\text{alkylene-X-R}^{32}$  [wherein  $\text{X}$  is  $-\text{NR}^{33}$ -,  $-\text{O}-$ ,  $-\text{S}(\text{O})_{n4}$ -,  $-\text{CO}-$ ,  $-\text{COO}-$ ,  $-\text{OCO}-$ ,  $-\text{NR}^{33}\text{CO}-$ ,  $-\text{CONR}^{33}$ -,  $-\text{NR}^{33}\text{SO}_2$ -,  $-\text{SO}_2\text{NR}^{33}$ -,  $-\text{NR}^{33}\text{COO}-$ ,  $-\text{OCONR}^{33}$ -,  $-\text{NR}^{33}\text{CONR}^{34}$ , or  $-$



NR<sup>33</sup>SO<sub>2</sub>NR<sup>34</sup>- (where R<sup>33</sup> and R<sup>34</sup> are independently hydrogen, alkyl, or acyl and n<sub>4</sub> is 0-2) and R<sup>32</sup> is hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl] wherein said alkylene chain is optionally substituted with one to six halo and wherein the aromatic or alicyclic ring in R<sup>1a</sup> is optionally substituted with one, two, or three R<sup>e</sup> independently selected from alkyl, haloalkyl, alkoxy, hydroxy, haloalkoxy, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, amino, monsubstituted amino, disubstituted amino, or acyl.

12. The compound of any of the Claims 1-10 wherein:

R<sup>1a</sup> is 2-methylpropyl, 2,2-dimethylpropyl, 4,4-dimethylcyclohexylmethyl, 4-ethyl-4-methylcyclohexylmethyl, 4,4-diethylcyclohexylmethyl, 3,3-dimethylcyclohexylmethyl, 3,5-dimethylcyclohexylmethyl, 1-ethoxycarbonylpiperidin-4-ylmethyl, 1-methylpiperidin-4-ylmethyl, cycloheptylmethyl, cyclooctylmethyl, 3,3-dimethylbutyl, 3-methylbutyl, 2-cyclohexylethyl, 2,2,3-trimethylbutyl, 2-cyclohexyl-2-methylpropyl, 3,3-dimethylpentyl, 3-ethyl-3-methylpentyl, 2-(1-methylcyclohexyl)ethyl, tetrahydronaphthylmethyl, 2-tetrahydropyran-4-ylethyl, 2-(1-methylcyclopropyl)ethyl, 2-(1-methylcyclopropyl)-2-methylpropyl, 2-cyclopentylethyl, 2-cyclopentyl-2-methylpropyl, 4-isopropyl-4-methylcyclohexylmethyl, phenylmethanethiomethyl, phenylmethanesulfonylmethyl, dimethylaminomethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, morpholin-4-ylmethyl, thiomorpholin-4-ylmethyl, 1-oxo-thiomorpholin-4-ylmethyl, 1,1-dioxothiomorpholin-4-ylmethyl, tetrahydrothiopyran-4-ylmethyl, 1-oxotetrahydrothiopyran-4-ylmethyl, 1,1-dioxotetrahydrothiopyran-4-ylmethyl, 1-methylpiperazin-4-ylmethyl, benzyloxymethyl, n-butyl, ethoxymethyl, ethylthiomethyl, ethylsulfonylmethyl, ethylsulfonylmethyl, isopropylthiomethyl, isopropylloxymethyl, 2-dimethylaminoethyl, 2-piperidin-1-ylethyl, 2-pyrrolidin-1-ylethyl, 2-methylthioethyl, 2-methylsulfinylethyl, 2-methylsulfonylethyl, *tert*-butylthiomethyl, *tert*-butylloxymethyl, benzyl, 4-methoxybenzyl, imidazol-4-ylmethyl, 4-dimethylaminobutyl, indol-3-ylmethyl, 2-dimethylaminocarbonylethyl, 2-pyrrolidin-1-ylcarbonylethyl, dimethylaminocarbonylmethyl, pyrrolidin-1-ylcarbonylmethyl, methoxycarbonylmethyl, 2-fluorophenylmethanesulfonylmethyl, 2-chlorophenylmethanesulfonylmethyl, 2-nitrophenylmethanesulfonylmethyl, 2-cyanophenylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, 2-fluorophenylmethane-thiomethyl, 2-chlorophenylmethanethiomethyl, 2-cyanophenylmethanethiomethyl, 2-nitrophenylmethanethiomethyl, cyclohexylmethanethiomethyl, cyclohexylsulfinylthiomethyl,



- cyclohexylmethanesulfonylmethyl, 3,4-dichlorobenzyl, 2-chlorobenzyl, 4-ethoxybenzyl, 4-nitrobenzyl, biphen-4-ylmethyl, naphth-1-ylmethyl, 2-methylbutyl, 1-methylpropyl, naphth-2-ylmethyl, 4-chlorobenzyl, 3-chlorobenzyl, 4-fluorobenzyl, indol-2-ylmethyl, 1-benzylimidazol-4-ylmethyl, 2-phenethyl, 4-hydroxybenzyl, 2-(4-hydroxyphenyl)ethyl, 4-ethyl-4-methylpiperidin-1-ylmethyl, 2-methylcyclohexylmethyl, 4-methoxycyclohexylmethyl, indol-1-ylmethyl, 1-methylpiperidin-2-ylmethyl, 2-bicyclo[2.2.1]hept-3-ylethyl, 8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethyl, bicyclo[3.2.1]oct-3-ylmethyl, bicyclo[3.1.1]hept-3-ylmethyl, 6,6-dimethylbicyclo[3.1.1]hept-3-ylmethyl, 6,6-dimethylbicyclo[3.1.1]hept-4-ylmethyl, 2-bicyclo[2.2.1]hept-1-ylethyl, bicyclo[2.2.1]hept-2-ylethyl, thiophene-2-sulfonylmethyl, 3-chloro-2-fluorophenylmethane-sulfonylmethyl, benzenesulfonylmethyl, phenylmethanesulfonylmethyl, 2-benzenesulfonylethyl, 2-(pyridin-2-ylsulfonyl)ethyl, 2-(pyridin-4-ylsulfonyl)ethyl, 2-phenylmethanesulfonyl-ethyl, oxypyridin-2-ylmethanesulfonylmethyl, 4-methoxyphenyl-methanesulfonylmethyl, *p*-tolylmethanesulfonylmethyl, 4-chlorophenylmethanesulfonylmethyl, *o*-tolylmethanesulfonylmethyl, 3,5-dimethylphenylmethanesulfonylmethyl, 4-trifluoromethylphenylmethanesulfonylmethyl, 4-trifluoromethoxyphenylmethanesulfonylmethyl, 2-bromophenylmethanesulfonylmethyl, naphth-2-ylmethanesulfonylmethyl, 3-methylphenylmethanesulfonylmethyl, 3-trifluoromethylphenylmethanesulfonylmethyl, 3-trifluoromethoxyphenylmethane-sulfonylmethyl, 4-fluoro-2-trifluoromethoxyphenylmethanesulfonylmethyl, 2-fluoro-6-trifluoromethylphenylmethanesulfonylmethyl, 2,6-difluorobenzyl, 1-methylcyclopentylmethyl, cyclohexyl, pyridin-4-ylmethyl, 3-chlorophenylmethanesulfonylmethyl, 2-trifluoromethylphenylmethanesulfonylmethyl, 4-*tert*-butylphenylmethanesulfonylmethyl, 2-fluoro-3-methylphenylmethanesulfonyl-methyl, 3-fluorophenylmethanesulfonylmethyl, 4-fluorophenylmethanesulfonylmethyl, 2,5-difluorophenylmethanesulfonylmethyl, 2,6-difluorophenylmethanesulfonylmethyl, 2,5-dichlorophenylmethanesulfonylmethyl, 3,4-dichlorophenylmethanesulfonylmethyl, 2-(1,1-difluoromethoxy)phenylmethanesulfonylmethyl, 3-cyanophenylmethane-sulfonylmethyl, 2-trifluoromethoxyphenylmethanesulfonylmethyl, 3-trifluoromethoxyphenylmethanesulfonylmethyl, 2,3-difluorophenylmethane-sulfonylmethyl, 2,5-difluorophenylmethanesulfonylmethyl, biphenyl-2-ylmethane-sulfonylmethyl, cyclohexylmethyl, 3-fluorophenyl-methanesulfonylmethyl, 2-pyridin-2-ylsulfonylethyl, 2-phenylsulfonylethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dichloro-3-phenylpropyl, 2,2,2-trichloroethyl, 2,2-dichloroethyl, 1,4-dimethylcyclopentylmethyl,



- 3,4-difluorophenylmethanesulfonylmethyl, 2,4-difluorophenylmethanesulfonylmethyl,  
 2,4,6-trifluorophenylmethanesulfonylmethyl, 2,4,5-trifluorophenylmethanesulfonylmethyl,  
 2,3,4-trifluorophenylmethanesulfonylmethyl, 2,3,5-trifluorophenylmethanesulfonylmethyl,  
 2,5,6-trifluorophenylmethanesulfonyl-methyl, 2-chloro-5-trifluoromethylphenylmethane-  
 5 sulfonylmethyl, 2-methylpropane-1-sulfonylmethyl, 2-fluoro-3-trifluoromethylphenyl-  
 methanesulfonylmethyl, 2-fluoro-4-trifluoromethylphenylmethanesulfonylmethyl,  
 2-fluoro-5-trifluoromethyl-phenylmethanesulfonylmethyl, 4-fluoro-3-trifluoromethyl-  
 phenylmethanesulfonylmethyl, 2-methoxyphenylmethanesulfonylmethyl,  
 3,5-bis-trifluoromethylphenyl-methanesulfonylmethyl, 4-difluoromethoxyphenylmethane-  
 10 sulfonylmethyl, 3-difluoromethoxyphenylmethanesulfonylmethyl, 2,6-dichlorophenylmethane-  
 sulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl, 3,5-dimethyl-  
 isoxazol-4-ylmethanesulfonylmethyl, 5-chlorothien-2-ylmethane-sulfonylmethyl,  
 2-[4-(1,1-difluoromethoxy)benzenesulfonyl]ethyl, 2-[2-(1,1-difluoromethoxy)benzene-  
 sulfonyl]ethyl, 2-[3-(1,1-difluoromethoxy)benzenesulfonyl]ethyl,  
 15 2-(4-trifluoromethoxybenzenesulfonyl)ethyl, 2-(3-trifluoromethoxybenzenesulfonyl)-ethyl,  
 2-(2-trifluoromethoxybenzenesulfonyl)-ethyl, (cyanomethylmethylcarbamoyl)methyl,  
 biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-ylethyl, 2-benzenesulfonylethyl,  
 isobutylsulfanylmethyl, 2-phenylsulfanylethyl, cyclohexylmethanesulfonylmethyl,  
 2-cyclohexylethanesulfonyl, benzyl, naphth-2-yl, phenylmethanesulfanylmethyl,  
 20 2-trifluoromethylphenylmethanesulfanylmethyl, phenylsulfanylethyl,  
 cyclopropylmethanesulfonylmethyl, 2-methylpropylsulfonylmethyl, 5-bromothien-2-ylmethyl,  
 3-phenylpropyl, 2,2-difluoro-3-phenylpropyl, 3,4,5-trimethoxy-phenylmethanesulfonyl-methyl,  
 2,2-difluoro-3-thien-2-ylpropyl, cyclohexylethyl, cyclohexylmethyl, cyclopentylmethyl, *tert*-  
 butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-  
 25 phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, or benzyloxymethyl;  
 and

$R^1$  is hydrogen.

13. The compound of any of the Claims 1-12 wherein:

- $R^3$  is hydrogen, alkyl, cycloalkyl, phenyl, benzyl, naphthyl, alkylSO<sub>2</sub>alkyl,  
 30 cycloalkylSO<sub>2</sub>alkyl, arylSO<sub>2</sub>alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,  
 piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,  
 imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl,  
 benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoisoxazolyl, benzoxazolyl or  
 amino; wherein the aromatic or alicyclic ring in  $R^3$  is optionally substituted by one, two, or three



R<sup>g</sup>;

each R<sup>g</sup> is independently alkyl, halo, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, cycloalkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, alkoxy, -COR (where R is alkyl), -OC(O)R (where R is alkoxy or aryl), aryloxy, benzyloxy, alkoxycarbonyl, aryloxy carbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, -NHCOR (where R is alkyl or aryl), alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkoxycarbonylamino, aryloxy carbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, where the aromatic or alicyclic rings in R<sup>g</sup> may be further optionally substituted by one, two or three R<sup>h</sup> independently selected from alkyl, aryl, cycloalkyl, alkoxy, haloalkyl, haloalkoxy, halo, hydroxy, carboxy, carboxamido, cyano, or nitro;

R<sup>2</sup> is hydrogen or methyl; and

R<sup>4a</sup> is hydrogen, alkyl, cycloalkyl, aryl, alkoxy, or hydroxy.

14. The compound of any of the Claims 1-12 wherein:

R<sup>3</sup> is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl, or amino where the nitrogen atom is mono or disubstituted with alkyl and wherein the aromatic or alicyclic rings in R<sup>3</sup> are optionally substituted with one, two, or three R<sup>g</sup> independently selected from methyl ethyl, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl imidazolyl, methoxy, acetyl, acetoxo, phenoxy, benzyloxy, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom is mono or disubstituted independently with



methyl, ethyl or phenyl, acetylamino, benzoylamino, methylthio, phenylthio, phenylsulfonyl, methylsulfonyl, methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom is mono or disubstituted independently with methyl or phenyl; wherein the aromatic or alicyclic rings in  $R^g$  are further optionally substituted with one, two, or three  $R^h$  independently selected from methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro, hydroxy, carboxy or carboxamido.

15. The compound of any of the Claims 1-12 wherein:

$R^3$  is hydrogen, methyl, carboxy, ethyl isopropyl, cyclopropyl, cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, furanyl, thientyl, thiazolyl, imidazolyl, pyridiny, pyraziny or amino where the nitrogen atom is optionally substituted with alkyl and wherein the aromatic or alicyclic rings in  $R^3$  are optionally substituted with one, two, or three  $R^g$  independently selected from methyl, chloro, fluoro, phenyl, thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, carbamoyl wherein the nitrogen atom is mono or disubstituted independently with methyl or phenyl, acetylamino, methylthio, phenylthio, phenylsulfonyl, methylsulfonyl, methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom is mono or disubstituted independently with methyl or phenyl;

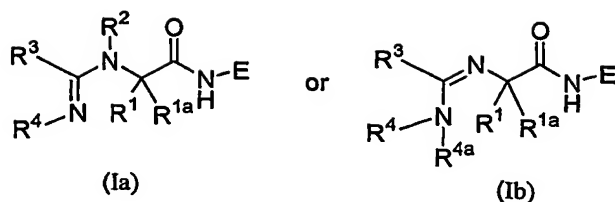
$R^{4a}$  is hydrogen, alkyl or alkoxy; and

$R^4$  is  $-S(O)_2R^{38}$  where  $R^{38}$  is phenyl or naphthyl optionally substituted with one, two, or three  $R^i$  independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, aminosulfonyl, acyl, amino, monosubstituted amino, disubstituted amino, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, or heterocyclyl where the aromatic or alicyclic ring in  $R^i$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl.

16. The compound of any of the Claims 1-15 where  $R^4$  is  $-S(O)_2R^{38}$  where  $R^{38}$  is phenyl optionally substituted with one, two, or three  $R^i$  independently selected from alkyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, alkylthio, alkylsulfonyl, aminosulfonyl, acyl, amino, monosubstituted amino, disubstituted amino, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl, heteroaryl, or heterocyclyl where the aromatic or alicyclic ring in  $R^i$  is optionally substituted with one or two substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, alkylamino, dialkylamino, carboxy, or alkoxycarbonyl.

17. A compound of formula:





wherein:

$R^1$ ,  $R^2$ , and  $R^{4a}$  are hydrogen;

$R^{1a}$  is cycloalkylalkyl wherein the alicyclic ring is optionally substituted with alkyl, heteroaralkyl, or -alkylene-S(O)<sub>n4</sub>-R<sup>32</sup> where n4 is 0 to 2 and R<sup>32</sup> is aralkyl where the aromatic ring is optionally substituted with haloalkoxy;

$R^3$  is hydrogen, alkyl, heterocyclyl, or alkylthio;

$R^4$  is phenylsulfonyl;

E is -CHR<sup>6</sup>COR<sup>10</sup> where R<sup>6</sup> is alkyl and R<sup>10</sup> is heteroaryl optionally substituted with alkyl or aryl, -CH<sub>2</sub>CN, or -CR<sup>5a</sup>R<sup>6a</sup> where R<sup>5a</sup> and R<sup>6a</sup> together with the carbon atom to which they are attached form cycloalkylene or heterocycloalkylene; or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any of the Claims 1-17 in admixture with one or more suitable excipients.

19. A method for treating a disease in an animal mediated by cysteine proteases which method comprises administering to the animal a therapeutically effective amount of a compound of any of the Claims 1-17.

20. The method of Claim 19 wherein the disease is psoriasis.